BIOPESTICIDE REGISTRATION ACTION DOCUMENT

THYMOL
5-methyl-2-isopropyl-1-phenol
(**PC Code 080402)**

U.S. Environmental Protection Agency
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division
THYMOL
(PC Code 080402)

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I. EXECUTIVE SUMMARY

A. IDENTITY:

The technical grade active ingredient (TGAI) is a constituent of oil of thyme, a naturally occurring mixture of compounds in the plant *Thymus vulgaris* (thyme). The product chemistry data submitted by the registrant satisfies the requirement for product identity.

B. USE/USAGE

Thymol (5-methyl-2-isopropyl-1-phenol) is to be used in end-use products for use in beehives to control the varroa mite (*varroa destructor*). There is currently no manufacturing use registration for the technical grade of thymol (5-methyl-2-isopropyl-1-phenol).

C. RISK ASSESSMENT

No unreasonable adverse effects on humans or the environment are anticipated from aggregate exposure to thymol. This includes all anticipated exposures for which there is reliable information.

1. Human Health Risk Assessment

a. Toxicological Endpoints

Acceptable toxicity studies and waiver requests were submitted and reviewed. BPPD's reviews cite acute oral LD_{50} higher than 2 grams / kilogram (g/kg) which places thymol's acute oral Toxicity Category III. Corrosive effects were observed after exposure to the TGAI. This places thymol's primary dermal and eye irritations in a Toxicity Category I. The review also indicated the thymol is a Toxicity Category IV for acute inhalation. Finally, hypersensitivity tests indicated that thymol is a dermal sensitizer.

b. Human Exposure

Thymol is found in the naturally occurring herb Thyme *(Thymus vulgaris)*. Thyme is used as a food seasoning ingredient, and is generally recognized as a safe (GRAS) natural seasoning by te Food and Drug Administration (FDA) (21 CFR 182.10). Thyme oil also is recognized as a GRAS essential oil by FDA (21 CFR 182.20). As a result, a large numbers of humans have been and continue to be regularly exposed to the active ingredient via physical contact and in their diet with no known reports of adverse effects. In addition, exposures and health risks from the use of registered pesticides are expected to be low. Thus, the Agency does not expect the use of thymol on food crops to result in any harmful effects to humans.

c. Risk Assessment

The Biopesticides and Pollution Prevention Division (BPPD) has not identified any subchronic, chronic, immune, endocrine, or non-dietary exposure issues as they may affect children and the general U.S. population. Thymol is a constituent of a mixture of organic compounds known to be rapidly degraded in the environment to elemental compounds. No toxicological endpoints have

been identified, and there is limited exposure to this product when used according to the label instructions. The Agency has considered thymol in light of the relevant safety factors in the Food Quality Protection Act (FQPA) of 1996 and under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and has determined that there will be no unreasonable adverse effects from the use of this product.

2. Ecological Risk Assessment

a. Ecological Toxicity Endpoints

No toxic endpoints were identified.

b. Ecological Exposure

As stated above, thymol is a naturally-occurring plant in the environment. The end-use product will be placed inside the beehives. As a result, exposure and, therefore, health risks to no-target aquatic and terrestrial organisms from the use of thymol is unlikely to occur nor result in addition of exposure and residues to the environment that are above pre-existing background levels

c. Risk Assessment

It is highly unlikely that the use of thymol will result in any adverse effect on terrestrial and aquatic non-target organisms. The active ingredient is a natural component of a commonly found in a plant. As a result, BPPD believes that the use of the thymol according to label use directions, should result in no significant adverse effects to wildlife.

D. DATA GAPS / LABELING RESTRICTIONS

There are no data gaps or labeling restrictions. Because of the end-use product's Toxicity Category I for eye irritation, some restrictions and precautionary labeling are required to mitigate risks associated with the proposed uses (see Labeling Rationale for details).

II. OVERVIEW

A. ACTIVE INGREDIENT OVERVIEW

Common Name: Thymol; Thyme camphor; Thymic acid

Chemical Name: 5- Methyl-2-(1-Methylethyl)phenol

Trade and Other Names: Thymocide; Topps

OPP Chemical Code: 080402

CAS Registry Number: 89-83-8

Empirical Formula: $C_{10}H_{14}O$

Molecular Formula: $(CH_3)_2CHC_6H_3(CH_3)OH$

Basic Manufacturer:

Vita (Europe) Limited
21/23 Wote Street
Basingstoke, Hants RG 21 7NE
United Kingdom

B. USE PROFILE

The following, is information on the proposed uses with an overview of use sites and application methods.

Type of Pesticide: Miticide

Use Sites: Beehives

Target: Varroatosis due to the mite *Varrroa destuctor*

Formulation Types: Slow release gel matrix

Method and Rates of Application: In the hive. Place a piece of wax sheet, cardboard or plastic sheet (approximately 4" x 4") centrally on top of the brood frames as a treatment tray. Using the dosing tools (scoop and spatula), apply the first dose of 50 g gel from the tub onto the tray. Ensure the scoop is full and level off the excess with the spatula. Use the spatula to scrape the gel to an even thickness over the tray area with the spatula. After two weeks apply the second dose of 50 g gel following the same procedure. Leave the product in the colony until it totally disappears from the tray or until the supers are installed, whichever is sooner. Small and wintering bee colonies and nuclei may require one dose of 25 g gel only, left in place until the product disappears from the tray. Dose out 50 g onto the treatment tray as before and cut in half

Use Practice Limitations:

1. Do not treat during honey flow.
2. Do not feed colonies during the treatment. The treatment can be performed immediately after the removal of the supers.
3. Do not use the product when the maximum daily temperature is lower than 60˚F or when the colony activity is very low.
4. Do not use the product when the maximum daily temperature is above

105°F.

Timing: The efficacy of the end-use product is maximized if the product is used in late summer after the honey harvest (when the amount of brood present is diminishing). However, in the case of severe infestations, the end-use product can also be used during springtime, when temperatures are above 60°F.

C. ESTIMATED USAGE

None used yet since this will be the first registered product.

D. DATA REQUIREMENTS

The data requirements for granting this registration under Section 3(c)(5) of FIFRA have been reviewed by BPPD. The mammalian toxicology and ecological effects data requirements for thymol have been fulfilled. Product analysis data requirements are adequately satisfied.

E. REGULATORY HISTORY

Products containing thymol were originally registered in 1964 for use as repellents for domestic animals. Subsequently, thymol-containing pesticides were approved for use as aciricides, fungicides and anti-microbials.

In September of 1993, the EPA issued a Reregistration Eligibility Decision (RED) for thymol. At that time the Agency concluded that thymol is an active ingredient that should be considered for a broad waiver of generic data requirements.

On July 17, 2003, Vita (Europe) Limited submitted a section 3 application and supporting documents to register the product Apiguard containing 25% of the active ingredient thymol. The end-used product is proposed to be used in the beehives to control Varroa mites.

A notice of filling a pesticide petition to establish a tolerance for the acaricide thymol, was published in the Federal register on April 27, 2005 (Volume 70, Number 801).

F. CLASSIFICATION

In 1997, the Biochemical Classification Committee determined that thymol is a biochemical pesticide because it is naturally occurring and it is used in foods and pharmaceuticals.

G. FOOD CLEARANCES/TOLERANCES

Thymol currently has an time-limited exemption from the requirement of a tolerance (§180.1240) in or on honeycomb in connection with use of the pesticide under section 18 emergency exemptions granted by EPA. Time limited exemptions from the requirement of a tolerance for residues of thymol

expired on June 30, 2007. Residues for the biochemical pesticide thymol, are exempt from the requirement of tolerance when used on honey, honeycomb and honeycomb with honey. The final rule was published in the Federal Register of January 18, 2006 (Volume 71; Number 11).

III. SCIENCE ASSESSMENT

A. PHYSICAL/CHEMICAL PROPERTIES ASSESSMENT

All product chemistry data requirements for thymol are satisfied.

Product Identity and Mode of Action

a. Product Identity:

Thymol is a colorless to white (MRID 46485601) cystalline solid (MRID 46485601) that smells like thyme (NOAA MSDS), is stable under ordinary conditions of use and storage (NOAA MSDS), has a neutral pH in alcohol (National Library of Medicine SIS ChemiID Plus), is not an oxidizer or reducer, melts at 48 - 51.5°C (MRID 46485601, MSDS dated November 15th 2001, National Library of Medicine SIS ChemiID Plus, NOAA MSDS), boils at 232.5-233°C (MSDS dated November 15th 2001, National Library of Medicine SIS ChemiID Plus, NOAA MSDS), has a specific gravity of 0.97 @ 25°C/4°C (NOAA MSDS), a dissociation constant of 10.62 @ 20°C (National Library of Medicine SIS ChemiID Plus), a partition coefficient of 3.3-3.34 (Log Kow; MSDS dated November 15th 2001, National Library of Medicine SIS ChemiID Plus, EPA 2001), water solubility of 900mg/L @ 20°C or 0.1g/100g water @ 25°C (National Library of Medicine SIS ChemiID Plus, NOAA MSDS), and vapor pressure of 0.0022 mm Hg @ 25°C, 12.7 Pa @ 40°C, and 1mm Hg @ 64°C (National Library of Medicine SIS ChemiID Plus, NIH Toxnet, NOAA MSDS).

b. Mode of Action:

Thymol is the active ingredient in the currently registered end-use product (EP) and is applied as a gel in trays to beehives to control and suppress parasitic varroa mites.

2. Food Clearances/Tolerances

Thymol currently has an time-limited exemption from the requirement of a tolerance (§180.1240) in or on honeycomb in connection with use of the pesticide under section 18 emergency exemptions granted by EPA. Time limited exemptions from the requirement of a tolerance for residues of thymol expired on June 30, 2007. Residues for the biochemical pesticide thymol, are exempt from the requirement of tolerance when used on honey, honeycomb and honeycomb with honey. The final rule was published in the Federal Register of January 18, 2006 (Volume 71; Number 11).

3. Physical And Chemical Properties Assessment

The physical and chemical characteristics of the TGAI were submitted to support the registration of the end-use product Apiguard. There are summarized in Table 1.

Table 1. Product chemistry data requirements:

GUIDELINE NO.	STUDY	RESULTS	MRID NO.
151B-10 (OPPTS 830.1100)	Product identity;	TGAI consists of 99 to 100% of thymol	46485601
151B-13 (OPPTS 830.1700)	Analysis of samples	99.9-100%	46485601
151B-15 (OPPTS 830.1750)	Certification of limits	100% ± 3% = 97-100%	46485601
151B-16 (OPPTS 830.1800)	Analytical method	Gas liquid chromatography	46485601
151B-17	PHYSICAL / CHEMICAL PROPERTIES FOR THE TGAI and End-Use Product (EP)		
151B-17(a) (OPPTS 830.6302)	Color	TGAI: colorless to white	46485601
151B-17(b) (OPPTS 830.6303)	Physical State	TGAI: Crystalline	46485601
151B-17(C) (OPPTS 830.6304)	Odor	thyme like odor	NOAA MSDS
151B-17(d) (OPPTS 830.7200)	Melting point	50.1ºC, 49.5ºC, 51.1ºC, 48-51ºC, 51ºC	46485601, MSDS dated Nov. 15, 2001, National Library of Medicine SIS ChemiID Plus, NOAA MSDS; Barrat 1996
151B-17(e) (OPPTS 830.7220)	Boiling point	Not a liquid	not appropriate for this TGAI
151B-17(f) (OPPTS 830.7300)	Density/Specific gravity	Specific gravity 0.91 @ 25ºC/4ºC	NOAA MSDS
151B-17(g) (OPPTS 830.7840)	Solubility	900 mg/L @ 20ºC	National Library of Medicine SIS ChemiID Plus, NOAA MSDS
151B-17(h) (OPPTS 830.7950)	Vapor Pressure	0.0022 mmHg @ 20ºC	National Library of Medicine SIS ChemiID Plus, NOAA MSDS, NIH Toxnet

151B-17(I) (OPPTS 830.7000)	pH	Neutral in alcohol	National Library of Medicine SIS ChemiID Plus
151B-17(j) (OPPTS 830.6313)	Stability	Stable	NOAA MSDS
151B-17(k) (OPPTS 830.6315)	Flammability	Not Required for TGAI	
151B-17(l) (OPPTS 830.6317)	Storage stability	Not Required for TGAI	
151B-17(m) (OPPTS 830.7100)	Viscosity	Not required for TGAI	
151B-17(n) (OPPTS 830.6319)	Miscibility	Not required for TGAI	
151B-17(o) (OPPTS 830.6320)	Corrosion characteristics	Not required for TGAI	
151B-17(p) (OPPTS 830.7550)	Octanol/water partition coef.	Log Kow = 3.30@ 20ºC	MSDS dated Nov. 15, 2001, National Library of Medicine SIS ChemiID Plus; Barrat 1996

B. HUMAN HEALTH ASSESSMENT

Thymol is a component of many non-pesticidal consumer products currently marketed in the United States. Thymol is listed as a food additive by the Food and Drug Administration (21 CFR 172.515; synthetic flavoring substances and adjuvants). Thymol is rapidly degraded in the environment to elemental constituents by normal biological, physical, and/or chemical processes that can be reasonably expected to exist where the pesticide is applied. The phenols of thymol are considered GRAS as set forth in 21 CFR 172.515 (synthetic flavoring substances and adjuvants).

The information submitted in support of the application for registration of Apiguard and the technical grade active ingredient thymol adequately satisfies the requirements set forth in 40 CFR 158.690 (c) for biochemical pesticides. The overall toxicological risk from human exposure to thymol is considered negligible.

1. Toxicology Assessment

a. Acute Toxicity

Acute oral toxicity - rat **(870.1100):**. The oral LD50 of thymol (5-methyl-(methylethyl) phenol; CAS# 89838) has been reported in ERMA (2005) and Sax (1984) to be 980, 640-1800, and 880 mg/kg in rats, mice, and guinea pigs respectively. The lowest reported oral LD_{50} concentration for

thymol (640 mg/kg in mice) was chosen to determine the acute oral Toxicity Category. This concentration places thymol conservatively into **Toxicity Category III** for acute oral effects.

Acute dermal toxicity - rat **(870.1200):** Calculated dermal LD_{50}s for technical thymol (Reference 2) are similar to that (>2000mg/kg) reported by the Environmental Risk Management Agency (ERMA, 2005) of New Zealand and Anonymous (2000). The lowest calculated dermal LD_{50} concentration for thymol (1049 mg/kg in mice) was chosen to determine the acute dermal Toxicity Category. This concentration places thymol conservatively into Toxicity Category II

Acute inhalation toxicity **(870.1300):** The waiver rationale for acute inhalation toxicity is based upon information from the U.S. Food and Drug Administration Center for Drug Evaluation and Research and other peer reviewed publications. Thymol is added to the anesthetic halothane as a preservative (0.01%) and is considered inactive (by FDA. 1997) at this concentration. Halothane is used to anesthetize dogs, cats, and other non-food animals for periods sometimes exceeding 4 hours. Anesthetic induction concentrations can typically reach approximately 5%. Calculation of the exposure from these factors yields a thymol atmospheric concentration of 5mg/L, at which permanent pathological effects on the anesthetized patients are not expected. Since this theoretical concentration is greater than 2 mg/L (the lower limit for Toxicity Category IV) thymol can be conservatively placed into Toxicity Category IV for acute inhalation toxicity for technical thymol.

Primary eye irritation - rabbit **(870.2400):** The test material caused corneal opacity which persisted to the final observation at day 28. Conjunctival irritation persisted to day 14, and iritis resolved by day 7. The test material is a severe eye irritant, and can be placed in Toxicity category I.

Primary dermal irritation - rabbit **(870.2500):** Data submitted states that thymol is corrosive to the skin. As a result, thymol can be placed in Toxicity Category I.

Skin sensitization (Maximization test) - guinea pig **(870.2600):** The waiver rationale for skin hypersensitivity is based on information presented in Hostynek and Magee (1997). Using quantitative structure activity relationships, Hostynek and Magee predicted that thymol is a dermal sensitizer. These results contrast that previously reported in the Federal Register (2003), Anonymous (2000), and ERMA (2005).

b. Mutagenicity, Developmental Toxicity, and Immune Response

Genotoxicity and mutagenicity studies were submitted as waiver rationales for genotoxicity (870.5000). These, in combination with other peer-reviewed publications retrieved by EPA, support the respective data requirement for the TGAI.

Thymol has been reported to be non-mutagenic in multiple Ames tests (strains TA97, TA98, and TA100 w and w/out metabolic transformation with S9 incubation (Azizan and Blevins, 1995; MRID 46282801; Stammati et al., 1999), but positive in unscheduled DNA synthesis (liquid scintillation), sister chromatid exchange, and cell transformation tests in Syrian hamster embryo cells in culture (Zani et al., 1991, MRID 46282802; ERMA, 2005; Tsutsui, 1987). In addition, thymol does not induce chromosomal aberrations in Allium cepa (Grant, 1982). Steam distilled extracts of three species of *Thymus* (*capitatus, citriodorus, vulgaris*) also were negative for DNA damaging activity and mutagenicity in the Ames test (strains TA1535, TA1537, TA98, and TA100 with and w/out metabolic activation). They were also non-mutagenic in a salmonella/microsome assay, did not induce the formation of micronuclei in mice, even when orally dosed in the toxic range (1100 mg/kg

bw). Further, in the A/He strain of mice, thymol did not increase the incidence of spontaneous lung tumors following repeated intraperitoneal dosing (Anonymous, 2000). Overall, the weight of evidence suggests that thymol is not genotoxic or mutagenic.

The waiver rationale for immune response (870.3550) is based upon information presented in a peer-reviewed publication (Hagan et al., 1967). In the subchronic study, no effects were seen in the thymus, spleen, lymph nodes, white cell counts, red cell counts, hemoglobin counts, or hematocrits following the dosing of rats with 1000 or 10000mg/kg of food grade thymol for 19 weeks

Mammalian toxicity data for thymol is summarized in Table 2.

Table 2. Toxicity data requirements

GUIDELINE NO.	STUDY	RESULTS	MRID NO.
TIER I			
152-10 (OPPTS 870.1100)	Acute oral toxicity	LD_{50} is 640 mg/Kg Toxicity; Toxicity Category III	National Library of Medicine SIS ChemiID Plus; NIOSH RTECS; Stammati et.al, 1999; Aldrich Chemical Corp. MSDS.
152-11 (OPPTS 870.1200)	Acute dermal toxicity	LD50 is 1049 mg/kg; Toxicity Category II	EPA Thymol RED; ERMA (2005)
152-12 (OPPTS 870.1300)	Acute inhalation toxicity	Inhalation LD_{50} is > 5 mg/L; Toxicity Category IV	Food and Drug Administration, April 10, 1997, NADA, Freedom of Information Summary, p3.
152-13 (OPPTS 870.2400)	Primary eye irritation	Corrosive; Toxicity Category I	cited in NIOSH RTECS; ERMA 2005
152-14 (OPPTS 870.2500)	Primary dermal irritation	Corrosive; Toxicity Category I	cited in NIOSH RTECS; Barrat 1996
152-15 (OPPTS 870.2600)	Dermal sensitization	Sensitizer	Hostyneck and Magee, 1997
152-17 (OPPTS 870.5000)	Genotoxicity	Negative for mutagenesis/genotoxicity based on weight of evidence	Azizian and Blevins, 1995; Zani et al., 1990 Stammati et al., 1999; Evrim et al. 2003; ERMA 2005

152-18 (OPPTS 870.3550)	Immune response	No sub-chronic immune effects	Hagen et al., 1967

c. Effects on the Endocrine Systems

EPA is required under section 408(p) of the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Thymol is not a known endocrine disruptor nor is it related to any class of known endocrine disruptors. Thus, there is no impact via endocrine-related effects on the Agency's safety finding set forth in this document for thymol.

2. Dose Response Assessment

No toxicological endpoints are identified.

3. Dietary Exposure and Risk Characterization

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

a. Food.

Thymol is found naturally in thyme herb (e.g., *Thymus vulgaris*, *T. zygis*). Thyme is used as a food seasoning ingredient, and is generally recognized as a safe (GRAS) natural seasoning by FDA (21 CFR 182.10). Thyme oil also is recognized as a GRAS essential oil by FDA (21 CFR 182.20). The volatile oil component of thyme herb is about 2% to 5% content, and thyme oil is reported to contain from 30% to 75% thymol, and even up to 90%. Thymol may be safely used in foods as a synthetic flavoring substance when used in the minimum quantity to produce the intended effect (21 CFR 172.515). Levels of thymol reported in foods where it is permitted as a direct food additive have been stated as 44 ppm in ice cream, ices, etc.; 2.5 ppm to 11 ppm in non-alcoholic beverages; 9.4 ppm in candy, 5 ppm to 6.5 ppm in baked goods, and 100 ppm in chewing gum. Thymol is a natural component of lime blossom honey, where the maximum thymol content has been determined to be 0.16 mg/kg.

European studies using Apiguard in bee hives *during honey flow* demonstrated that thymol residues in honey accumulated up to 4.61 mg thymol/kg honey after 2 days of exposure. This represents a worst case scenario for potential residues because residue incorporation into honey could have occurred directly from the Apiguard tray. Thymol residues in wax were not considered in this dietary assessment because wax is not known to be a dietary foodstuff.

EPA estimated the dietary exposure to U.S. subpopulations using the maximal thymol

residue level from the European studies (4.61 mg/kg) and compared it to estimated exposures resulting from thymol in other foodstuffs (ice cream @ 44 mg/kg, yellow cake @ 6.5 mg/kg, cola beverage 2 11 mg/kg, and caramel candy @ 9.4 mg/kg). Ingestion rates for honey and the foodstuffs were obtained from the FDA Total Diet Study (1990). Body weights for the respective populations were derived from the EPA Exposure Factors Handbook (1997).

Calculated thymol exposures from honey were substantially less than that from the food stuffs Normalized data showed that the U.S. general population is potentially exposed to 938 times more thymol from the consumption of ice cream, yellow cake, cola beverages, and caramel candy than from thymol consumed in honey. Similarly, calculations show that the population with highest exposure (6 year old child) is potentially exposed to 279 times more thymol from the consumption of other foodstuffs than from thymol in honey. Male adults (60-65 years old) share a similar level of exposure with 251 times more exposure to thymol from foodstuffs other than honey. These calculations illustrate that thymol residues in honey will not contribute significantly to the dietary burden of thymol.

b. Drinking water exposure

No drinking water exposure is expected from the pesticidal use of thymol which is confined to placement in beehives. Thymol is currently registered for use on ornamental plants, shrubs and grasses so there is some potential for exposure to water. However, thymol is a constituent of a mixture of organic compounds known to be rapidly degraded in the environment to elemental compounds by normal biological, physical and/or chemical processes. In the RED, the Agency concluded that the registered uses of thymol will result in negligible exposure of the environment and nontarget organisms (refer to page 7 of the RED). Therefore, thymol is not expected to be found in drinking water.

4. Occupational, Residential, School and Day Care Exposure and Risk Characterization

Human exposure to thymol is not expected in residential, school and day care areas.

a. Occupational Exposure

The end-use product is used as a slow release gel matrix presented in a tray which is placed in a bee hive. The possibility for dermal, eye and inhalation exposure, is mitigated as long as the product is used according to label directions, which requires the use of protective equipment, the restricted entry interval into treated areas.

b. Residential, School and Day Care Exposure and Risk Characterization

No indoor residential, school, or day care uses currently appear on proposed labels. Human exposure to thymol should not occur in these areas.

6. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children

A. U.S. population. There is reasonable certainty that no harm will result from aggregate exposure to residues of thymol to the U.S. population, infants, and children. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency has arrived at this conclusion based on the fact that the plant is a part of the human diet in certain areas of the world with no reported adverse effects, and that humans have had frequent physical contact with thyme and plants treated with thymol no negative health effects.

B. Infants and children. FFDCA section 408 provides that EPA shall apply an additional tenfold margin of exposure (also referred to as a margin of safety) for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database unless EPA determines that a different margin of exposure will be safe for infants and children. Margins of exposure are often referred to as uncertainty or safety factors. In this instance, based on all available information, the Agency concludes that thymol is non-toxic to mammals, including infants and children. Because there are no threshold effects of concern to infants, children and adults when thymol is used as labeled, the provision requiring an additional margin of safety does not apply. As a result, EPA has not used a margin of exposure approach to assess the safety of thymol.

7. Cumulative exposure to substances with a common mechanism of toxicity.

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider ``available information'' concerning the cumulative effects of a particular pesticide's residues and ``other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether thymol has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, thymol does not appear to produce a toxic metabolite produced by other substances. For the purposes of this exemption from the requirement of a tolerance, therefore, EPA has not assumed that thymol has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the final rule for Bifenthrin Pesticide Tolerances (62 FR 62961, November 26, 1997).

8. Cumulative Effects

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish an exemption from a tolerance, the Agency consider “available information concerning the cumulative effects of a particular pesticide’s residues and other substances that have a common mechanism of toxicity.” These considerations include the possible cumulative effects of such residues on infants and children.

Common mechanisms of toxicity are not relevant to a consideration of cumulative exposure to thymol because it is not toxic to mammalian systems. Thus, the Agency does not expect any cumulative or incremental effects from exposure to residues of thymol when

applied/used as directed on the label and in accordance with good agricultural practices.

9. Risk Characterization

The Agency has considered thymol in light of the relevant safety factors in FQPA and FIFRA. A determination has been made that no unreasonable adverse effects to the U. S. population in general, and to infants and children in particular, will result from the use of thymol when label instructions are followed.

C. ENVIRONMENTAL ASSESSMENT

1. Ecological Effects Hazard Assessment

Vita (Europe) International submitted waiver requests for avian acute oral (850.2100), avian dietary (850.2200), freshwater fish LC50 (850.1075), and freshwater invertebrate LC50 (850.1010) toxicity testing. BPPD approved the waiver requests and agrees with the argument that exposure of non target organisms is unlikely since the product will be placed on a tray inside closed beehives. Moreover, thymol has a low mammalian toxicity and degrades rapidly in the environment.

1. Environmental Fate and Ground Water Data

Environmental exposure assessments on biochemical pesticides are not performed unless significant human health or ecological effects issues arise in the Tier I studies for either of these disciplines (40 CFR §158.690 (c) and (d)). Since Tier II studies were not triggered, there is no requirement for environmental fate data.

2. Ecological Exposure and Risk Characterization

Thymol is found in the naturally occurring herb Thyme *(Thymus vulgaris).* Thyme is used as a food seasoning ingredient, and is generally recognized as a safe (GRAS) natural seasoning by the Food and Drug Administration (FDA) (21 CFR 182.10). Thyme oil also is recognized as a GRAS essential oil by FDA (21 CFR 182.20). As a result, a large numbers of humans and other organisms have been and continue to be regularly exposed to the active ingredient via physical contact and in their diet with no known reports of adverse effects.

Exposures and health risks from the use of registered pesticides are expected to be low. Moreover, thymol will be used in slow release gel matrix presented in tray that regulates the liberation of thymol in the honeybee colony. As a result, no toxicology or environmental fate and effects data were deemed necessary for this registration.

Precautionary labeling of Apiguard stipulates, "This product is toxic to aquatic invertebrates. Do not apply directly to water, areas where surface water is present or to intertidal areas below the mean high water mark. Drift or runoff from treated areas may be hazardous to aquatic organisms in neighboring areas. Do not contaminate water when disposing of equipment washwaters."

The waiver requests for submitted data are summarized in Table 3.

TABLE 3. Non-Target Toxicity Studies - Tier I Guideline Requirements			
Guideline No.	**Study**	**Result**	**MRID**
154-6 (OPPTS 850.2100)	Avian acute oral	Waived. No anticipated exposure	Administrative materials
154-7 (OPPTS 850.2200)	Avian dietary	Waived. No anticipated exposure.	Administrative materials.
154-8 (OPPTS 850.1075)	Freshwater fish LC_{50}	Waived. No anticipated exposure . *P. promelas*, 96h LC 50 - 3.2 mg/L	Administrative materials. ECOTOX database
154-9 (OPPTS 850.1010)	Freshwater invertebrate LC_{50}	Waived. No anticipated exposure. D. magna 96h LC50 - 1.7 mg/L	Administrative materials. ECOTOX database.

D. EFFICACY DATA

No efficacy data are required, because no public health uses are involved.

IV. RISK MANAGEMENT DECISION

A. DETERMINATION OF ELIGIBILITY FOR REGISTRATION

Section 3(c)(5) of FIFRA provides for the registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted comply with the requirements of FIFRA; (c) it will perform its intended function without unreasonable adverse effects on the environment and (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

To satisfy criteria "A" above, thymol is not expected to cause unreasonable adverse effects when used according to label instructions. Criteria "B" is satisfied by the current label and by the data presented in this document. It is believed that this new pesticidal active ingredient will not cause any unreasonable adverse effects, will extend the life and usefulness of ornamentals as claimed satisfying Criteria "C". Criteria "D" is satisfied by the data submitted and the low exposure to the product when used according to label directions.

Therefore, thymol is eligible for registration. Registered use is listed in Table 4, Appendix A.

B. REGULATORY POSITION

1. Conditional/Unconditional Registration

All data requirements are fulfilled and BPPD recommends unconditional registration of thymol.

2. CODEX Harmonization

There are no Codex maximum residue levels established for thymol.

3. Non-food Re/Registrations

Thymol is currently registered for use as a disinfectant and animal repellent.

4. Risk Mitigation

There are no significant risk issues. Risks to applicators and handlers are mitigated by protective clothing requirements and re-entry restrictions.

5. Endangered Species Statement

Currently, the Agency is developing a program (The Endangered Species Protection Program) to identify all pesticides whose use may cause potential adverse impacts on endangered and threatened species and their habitats. To aid in the identification of threatened and endangered species and their habitats, several companies have formed an Endangered Species Task Force (EST) under the direction of the American Crop Protection at the subcounty level, and, particularly, if an endangered species occurs in areas where pesticides would be used. This information will be useful once the Endangered Species Protection Program has been implemented.

The Agency has no evidence to believe that any endangered or threatened species will be adversely affected if products containing thymol are used as labeled. The Agency has made a no effect finding for the use pattern of thymol. Thus, no labeling is required for endangered or threatened species at this time.

C. LABELING RATIONALE

It is the Agency's position that the labeling for apiguard containing 25% of thymol complies with the current pesticide labeling requirements.

1. Human Health Hazard

a. Worker Protection Standard

Any product whose labeling reasonably permits use in the production of an agricultural plant on any farm, forest, nursery, or greenhouse must comply with the labeling requirements of PR Notice 93-7, "Labeling Revisions required by the Worker Protection Standard (WPS), and PR Notice 93-11, "Supplemental Guidance for PR Notice 93-7, which reflect the requirements of EPA"s labeling regulations for worker protection statements (40 CFR part 156, subpart K). These labeling revisions are necessary to implement the Worker Protection Standard for Agricultural Pesticides (40 CFR part 170) and must be completed in accordance with, and within the deadlines specified in PR Notices 93-7 and 93-11. Unless otherwise specifically directed, all statements required by PR Notices 93-7 and 93-11 are to be on the product label exactly as instructed in those Notices.
The labels and labeling of all products must comply with EPA’s current regulations and requirements as specified in 40 CFR 156.10 and other applicable notices, such as, and including the WPS labeling.
Workers and handlers (including mixer/loaders, and applicators) applying this product must wear long sleeved shirt, long pants, shoes and socks, chemical resistant gloves and protective eyewear.

b. Non-Worker Protection Standard

No non-workers standard necessary since the product is placed inside beehives.

c. Precautionary Labeling

The Agency has examined the toxicological data base for Apiguard and concluded that the proposed

precautionary labeling (i.e. Signal Word, Statement of Practical Treatment and other label statements) adequately mitigates any risks associated with the proposed uses.

> **End-Use product Precautionary Labeling:** For Apiguard, "DANGER". Causes irreversible eye damage. Harmful if swallowed or absorbed through skin. Do not get in eyes, on skin, or on clothing. Wear protective eyewear such as goggles, face shield, or safety glasses. Wear chemical resistant gloves. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

d. Spray Drift Advisory

No spray drift advisory needed. The product is applied as a slow release matrix inside the beehive.

2. Environmental Hazards Labeling

> **End-Use Product Environmental Hazards Labeling:** This product is toxic to aquatic invertebrates. Do not apply directly to water, areas where surface water is present or to intertidal areas below the mean high water mark. Drift or runoff from treated areas may be hazardous to aquatic organisms in neighboring areas. Do not contaminate water when disposing of equipment washwaters.

3. Application Rate

It is the Agency's position that the labeling for the pesticide product containing Apiguard complies with the current pesticide labeling requirements. The Agency has not stipulated a maximum number of applications for the active ingredient.

Place a piece of wax sheet, cardboard or plastic sheet (approximately 4" x 4") centrally on top of the brood frames as a treatment tray. Using the dosing tools (scoop and spatula), apply the first dose of 50 g gel from the tub onto the tray. Ensure the scoop is full and level off the excess with the spatula. Use the spatula to scrape the gel to an even thickness over the tray area with the spatula. Ensure that there is a free space of at least ¼ inch between the top of the tray and the hive cover board, for example, by placing an empty super on top of the brood box. Close the hive.

After two weeks apply the second dose of 50 g gel following the same procedure. Leave the product in the colony until it totally disappears from the tray or until the supers are installed, whichever is sooner.

D. LABELING

(1) Product name: **Apiguard**

Active Ingredient:

Thymol..... . . . . 25.00%
Other Ingredients 75.00%

Total 100.00%

Signal word is "DANGER". Eye irritation warning is appropriate.

The product shall contain the following information:

- Product Name
- Ingredient Statement
- Registration Number
- "Keep Out of Reach of Children"
- Signal Word (DANGER)

V. ACTIONS REQUIRED BY REGISTRANTS

Reports of incidences of adverse effects to humans or domestic animals under FIFRA, Section 6(a)2 and incidents of hypersensitivity under 40 CFR Part 158.690(c), guideline reference number 152-16. There are no data requirements, label changes and other responses necessary for the reregistration of the end-use product since the product is being registered after November 1984 and is, therefore, not subject to reregistration. There are also no existing stocks provisions at this time.

VI. APPENDIX A

Table 4 lists the use sites for the product.

Table 4. Food Use Site Registration/Reregistration

Apiguard	Official date registered:
Use Sites	
Beehives	

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